REMARKS

The Official Action dated October 2, 2008 has been carefully considered. Submitted herewith is a Declaration under 1.132 that attests to the nonobvious differential impact of LPS versus IR-LPS on the targeted outcome of the instant inventive methods. It is believed that this secondary evidence addresses and overcomes the remaining issues raised by the Examiner and places the present application in condition for allowance. Reconsideration is therefore respectfully requested.

Claims 1-3, 5-18, and 20-25 remain pending while claims 1-3, 5, 10, 13, 17-18 and 22-25 are currently subject to examination.

35 USC § 103

The rejection of **claims 1-3, 5, 10, 13, 17-18 and 22-25** under 35 U.S.C. 103(a) as being unpatentable over Cochran et al. (PTO-892 mailed on 01/29/2008, Reference U) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) is maintained for reasons of record. Summarily, the Examiner asserts that Cochran teaches a process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (2-3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (E.coli LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during nasal aspiration) during maturation of the mammal (at 2-3 weeks), and also teaches that "recent studies raised the **intriguing hypothesis** that exposure to LPS may interact with the immune system in early life and produce a protective environment against the development of asthma and atopy.

The Examiner notes that Cochran fails to teach any benefit or differential benefit of "irradiation detoxified lipopolysaccharide" as recited in claims 1-3, 5, 10, 13, 17-18, and 22-25 "wherein exposure comprises at least weekly administration during maturation of the mammal" of claim 1; "wherein the irradiation-detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 kGy" in claim 2; "wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive immune effect in the resulting irradiation-detoxified lipopolysaccharide" in claim 3; "wherein the mammal is a human and during maturation is between 1 month and 2 years of age" of claim 13; "during maturation" is throughout the maturing life cycle of the mammal" of claim 17; "wherein administration is on a daily basis" of claim 18; "wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age" of claim 24; and exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irraditation-detoxified lipopolysaccharide at a concentration of 5-15 μg/ml" in claim 25.

The Examiner applies Previte for teaching the detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation to ostensibly eliminate lethality induced by its lethal determinants (which the Examiner asserts to be a result of changes in the structure), while retaining antigenticity (which the Examiner asserts to be via maintaining its Th1 stimulatory effect) and pyrogenicity. It is significant to note that Previte predates the primary reference by 35 years.

The Examiner asserts that no patentable weight may be assessed with respect to the functional limitation described by the recitation of "operable to stimulate the Th1 arm of the human's immune system" of claims 1 and 22; and "operable to stimulate the Th1 arm of the human's immune system while reducing interleukin 1 (IL-1) stimulation caused by the native form of the lipopolysaccharide derived from extracted bacterial endotoxin" of claim 25; and "by restoring normal immune system development" in claim 22. The Examiner further asserts that these are inherent properties of the reference irradiation-detoxified lipopolysaccharide.

Claims 1-3, 5, 10, 13, 17-19, 22-25 are included in the rejection as requiring no more than identification and determination of optimum modes and workable ranges involving only routine skill in the art.

The Examiner asserts that it would be obvious to practice the process taught by Cochran in humans of 1 month to 2 years of age and during the maturing life cycle of the mammal because Cochran suggests performing the process for decreasing development of allergic asthma in young children under 5 years of age implicitly. The Examiner further asserts that a person of ordinary skill would be motivated to use the irradiation detoxified lipopolysaccharide of Previte in processes for decreasing allergic asthma of Cochran et al. "**because the process should be safe" and without toxic effects for use in infants and children"**. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants "while still retaining antigenicity and pyrogenicity." The Examiner argues that it would be obvious to use a safer, less toxic form of LPS in a neonate or immature mammal.

The Examiner and Applicants have asserted and argued the same basic dissenting tenets for the last several office actions. In this latest action, the Examiner asserts that Applicant's arguments filed on 06/27/2008 have been fully considered, but are not found persuasive.

The Examiner's references and position may be distilled to the following: Cochran explores a hypothesized connection between early exposure to LPS and maturation of the immune system and in doing so hypothesizes administration of LPS to a newborn to reduce development of immune system sensitivities, and Previte discloses that irradiation of LPS may alter the native structure to reduce toxicity. The Examiner asserts that Cochran teaches all the affirmative steps of the instant methods and a person of ordinary skill in the art would be motivated to use the IR-LPS of Previte in the "method" of Cochran to decrease the known toxicity of native LPS.

Applicants arguments may be distilled to the following: Cochran fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Cochran uses LPS rather than IR-LPS. Second, Cochran teaches a one-time exposure during development while Applicants teach a continual exposure over a critical developmental period. Third, Cochran teaches application of LPS directly to the subject, whereas Applicants teach indirect exposure by application of IR-LPS to the environment. All of these elements are disclosed by Applicants as critical to the efficacy of the inventive method, yet the Examiner ignores the complete absence of the latter two, and applies Previte, a reference that teaches direct administration of IR-LPS to adult mammals to test for a decrease in toxicity, reporting death of nearly a third of the subjects 6 days after administration (see, e.g. Fig. 3), and "extensive

inactivation of antigenic antigenic components with increasing radiation dose (page 1611, second column, line 11-14).

With respect specifically to Previte, Applicants have argued that if it is true that the disclosure of Previte would guide an ordinary practitioner to the use of IR-LPS in the methods of Cochran (as the Examiner asserts), then Cochran himself would have employed IR-LPS since Previte was published 35 years prior to Cochran. However, Applicants note that not only does Previte fail to disclose or suggest the missing elements of administration across a developmental continuum and indirect exposure as the form of administration, Previte actually discloses retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner away from direct administration to a developmentally immature subject. Yet the Examiner expressly states (please note bolded type on page 3, above) that the motivation for using Previte's IR-LPS in Cochran is specifically because a practitioner would conclude based on the teachings of Previte that it would be safe for children and infants! Applicants respectfully demand to know where in Previte it is expressed or implied that the toxic effects of LPS and the retained toxic effects of IR-LPS are eliminated with respect to direct administration to children, infants, or even adults? In fact, Previte may be construed as supporting the thesis that results as to direct administration include that toxicity is retained, although diminished, and that antigenicity is decreased, although substantial decrease is temperature, dose and time dependent. Indeed, Previte expressly teaches "mean survival time was increased by vaccination with LPS but decreased toward control levels when the LPS had been exposed to 5 or 20Mrad. In general, the percentage of survivors, too, decreased similarly.

Previte admits that only mortalities recorded up to day 14 are reported, although inactivation of antigenicity peaks much later" (see, e.g. page 1611 second column).

The Examiner continues to stand firm on the position that because IR-LPS is the active, therefore all effects on the subjects are inherent. In taking this position, though, the Examiner fails to consider the distinguishing impact of the route of administration. There is simply no way for the Examiner to conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Applicants note that Previte supports this since Previte discloses full single dosing by direct administration which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on passive dosing over a development period by misting the environment without toxic effect. When entering the subject noninvasively and passively via breathing it is clear that parameters such as toxicity and antigenicity are altered.

Applicants have repeatedly argued that a differential effect also exists with respect to exposure to LPS versus IR-LPS and resulting impact on the developing immune system and later immune responsiveness. The Examiner counters that (1) this effect is of no moment since the motivation to combine is based on decreased toxicity so that it would be obvious to use IR-LPS in the methods of Cochran because it would be "safe for infants and children". As set forth in detail above, Applicants respectfully assert this argument as preposterous. The methods of both references involve direct administration of single doses. As disclosed by Previte this results in a completely unacceptable level of toxicity despite irradiation of the LPS. One cannot fathom a method being considered "safe" for infants where the survival rate is 7/10 at six days post-

challenge, a result disclosed as a good result by Previte (see Fig. 3, e.g.). Further, Applicants submit that bioequivalence simply does not exist where considering single high invasive dosing versus virtually constant low-level passive exposure and that this would be readily understood by a person of ordinary skill in the art. (2) The Examiner asserts that Applicants have argued but failed to provide any evidence of an unpredicted or heretofore unknown differential impact of IR-LPS over LPS (see, e.g. October 2 Office Action, page 13, third full paragraph).

Applicants therefore submit the Declaration submitted herewith and attested to by inventor Sandor Sipka, M.D. Ph.D. and executed on February 23, 2009. In the Declaration Dr. Sipka testifies as to experimental protocols and results relating to testing the difference in the *in vivo* immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (passively as a mist sprayed into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6).

Hence, Applicants submit that even in the event the Examiner maintains the position that a prima facie case exists on the basis of the reference, the Declaration constitutes secondary evidence of nonobviousness since it clearly demonstrates that specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580

(CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). The combined references fail to teach or suggest methods comprising more than a single treatment applied directly to the subject, whereas the method defined by the instant claims require a duration of passive administration/exposure by, e.g. repeated administration across a maturation period of the subject with application to the subject's living environment. While Cochran posits that certain data "appears" consistent with the original hypothesis that LPS confers a protective effect against allergic asthma, Cochran admits that the actual results fail to yield a disrupting in the Th1/Th2 balance, a disruption that Cochran teaches is implicated in restoring a normal Th1/Th2 balance to protect against the development of asthma. The secondary reference, Previte, which teaches single high doses of IR-LPS to adult subjects to investigate the relations between irradiation and retention of lethality and antigenicity, fails to overcome the deficiencies of Cochran. Previte actually discloses an unacceptably high death rate in subjects (a good result being 3 deaths out of 10 subjects) and that components of antigenicity relating to long terms adaptations of the immune system (such as that which would be necessary to protect against development of asthma) may be destroyed by the levels of radiation needed for detoxification sufficient to eliminate lethality. Hence, at least two important elements of the instant invention are completely unaddressed by the combined references: the passive administration and the continual administration across a developmental period.

Moreover, there is no motivation in either reference to combine the teachings, since Previte is directed to treatment of adult subjects and teaches retention of an unacceptable degree

of toxicity for medical uses, and further teaches against uses of IR-LSP for eliciting an adaptive immune response. Finally, importation of the IR-LPS of Previte into the Cochran protocol still fails to enable the present methods, which require more than a single exposure during a maturation period of the developing mammal and administration by application to the environment of the mammal."

For these reasons Applicants submit that instant claims 1-3, 5, 10, 13, 17-18 and 22-25 are nonobvious and patentable under 35 U.S.C. 103(a) over Cochran in view of Previte. Reconsideration is respectfully requested.

Claims 1-3, 5, 10, 13, 17-18 and 22-25 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Khan in view of Previte for the same reasons as set forth in the Office Action mailed on 01/29/2008 and reiterated in subsequent office actions. Summarily, the Examiner applies Khan for teaching "a process for decreasing development of allergic asthma (OVA induced asthma) comprising exposing an infant, neonatal or immature mammal maturing in an overly sterile environment shortly after birth (3 week old laboratory mice) to lipopolysaccharide derived from extracted bacterial endotoxin (LPS) by administering an aerosol spray composition of the mammal to a living environment/space (saline and air during intratracheal aspiration) during maturation of the mammal (at 3 weeks). The Examiner states that Khan discloses that "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma." The Examiner notes that Khan fails to teach IR-LPS, at least weekly administration during maturation of the mammal," a detoxification radiation level of from about 25 to about 150 kGy, " "wherein the irradiation changes the structure of the endotoxin while maintaining its Th1 stimulatory positive

immune effect in the resulting irradiation-detoxified lipopolysaccharide, " "wherein the mammal is a human and during maturation is between 1 month and 2 years of age, " "wherein administration is on a daily basis,' "wherein the mammal is a human infant and exposure comprises at least weekly administration from 1 month to 2 years of age," exposing a "human of up to about 2 years of age" and "wherein exposure comprises administration on an at least weekly basis of an aerosol spray composition comprising the irradiation-detoxified lipopolysacharied at a concentration of 5-15 μg/ml" in claim 25.

The Examiner applies Previte for teaching detoxification of isolated LPS of S. typhimurium, S. enteritidis and E. coli using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation and for teaching that "the detoxification eliminates lethality induced by its lethal determinants (changes the structure), while retaining antigenicity (maintaining its Th1 stimulatory effect) and pyrogenicity." With respect to these last ostensible teachings the Examiner asserts that these are disclosed inherently even though dosing, routes of administration, and maturation status of the subjects are all significantly different. With respect to "elimination" of lethality, the Examiner adopts the Previte term "elimination" to describe an improvement in survival rate although Previte fails to disclose an actual elimination and actually describes a survival rate of 7 out of 10 subjects as achieving target.

The Examiner argues that since Khan notes that "recent evidence has suggested that post-natal exposure to endotoxin may protect against the development of allergen sensitization and asthma," practice of the methods in humans of 1 month to 2 years of age and during maturation would be obvious. The Examiner argues that a person of ordinary skill in the art would have

been motivated to use the IR-LPS of Previte in the Khan process for decreasing allergic asthma because the process "should be safe and without toxic effects for use in infants and children."

Applicants' prior arguments may be summarized as follows: (1) Khan specifically notes that treatment with LPS did not affect allergen-induced airway hyperresponsiveness (AHR), and teaches that "airway exposure to LPS produces transient AHR and inflammation in developing mice and **does not appear to influence functional and immune responses induced by subsequent allergen sensitization**" (see Poster Board 219); (2) Khan is part of the same research team as Cochran and published these findings as inconsistent with the results/conclusions of Cochran, in particular with respect to impact on subsequent allergen sensitization; (3) Khan expressly teaches that LPS does not appear to influence the very responses sought to be elicited by the instant invention; (4) Previte fails to teach or suggest the immunostimulatory properties of irradiated LPS that underpin the instant inventive methods; and (5) Previte teaches retention of unacceptable morbidity at IR levels within the scope of the instant invention and suggests that the level of irradiation necessary to effectively detoxify LPS results in destruction of the components of antigenicity that may be related to eliciting a long term adaptive immune response.

Applicants further argue that a person of ordinary skill in the art seeking methods to decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocols of Cochran or Khan because Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate among the subjects. (Although the Examiner objects that Applicants may not define what is "acceptable", Applicants contend that a

positive death rate predictably due to the treatment, as disclosed by Previte for IR levels within the scope of the instant invention, would be universally understood as unacceptable and that no expert opinion need be procured to attest to this understanding). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000)."

Applicants argue that a person of ordinary skill in the art would not be guided by the teachings of Previte to use IR-LPS in the methods of Khan based on the motivation assessed by the Examiner - that it would be safe for children and infants. Indeed, Previte fails to consider administration to immature subjects and notes unacceptably high death rates among adult subjects where IR doses are low enough for retention of antigenicity. The Examiner argues that regardless of this, all primary references teach use of non-irradiated LPS and Applicants have failed to demonstrate any unexpected difference between LPS and IR-LPS specifically with respect to the targeted outcome of reducing . Hence, Applicants submit the attached Declaration by inventor Sipka attesting to the differential and unexpected impact of IR-LPS over LPS in in vivo studies testing assessing the targeted outcome of allergy prevention.

For this reason claims 1-3, 5, 10, 13, 17-18 and 22-25 are nonobvious and patentable under 35 U.S.C. 103(a) over Khan in view of Previte. Reconsideration is respectfully requested.

Conclusion

It is believed that the above represents a complete response to the remaining rejections under 35 U.S.C. §103 and places the present application in condition for allowance. Nonetheless, should the Examiner decide that issues remain unresolved she is urged to contact Applicants at the number listed below for expedited resolution. Reconsideration and an early allowance are otherwise respectfully requested.

Respectfully submitted,

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